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(71) **Applicant** *(for all designated States except US)*: ALGOS PHARMACEUTICAL CORPORATION [US/US]; 1333 Campus Parkway, Neptune, NJ 07753 (US).

(72) **Inventor; and**
(75) **Inventor/Applicant** *(for US only)*: CARUSO, Frank, S. [US/US]; 2 Bowling Green, Colts Neck, NJ 07722 (US).

(74) **Agents:** DILWORTH, Peter, G. et al.; Dilworth & Barrese, 333 Earle Ovington Boulevard, Uniondale, NY 11553 (US).

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(54) **Title:** COX–2 INHIBITORS IN COMBINATION WITH CENTRALLY ACTING ANALGESICS

(57) **Abstract**

A method of alleviating a pain state not associated with a cough condition is provided which comprises administering a cyclooxygenase–2 inhibitor and a centrally active analgesic selected from the group consisting of a narcotic analgesic selected from the group consisitng of codeine and hydrocodone; an agonist–antagonist analgesic and tramadol. A method and analgesic composition therefor is also provided for treating all pain states which comprises administering a cyclooxygenase–2 inhibitor and a centrally acting analgesic selected from the group consisting of a narcotic analgesic other than codeine and hydrocodone; an agonist–antagonist analgesic and tramadol.

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COX–2 INHIBITORS IN COMBINATION WITH CENTRALLY ACTING ANALGESICS

BACKGROUND OF THE INVENTION

This invention relates to a method and composition for alleviating pain. More particularly, this invention is concerned with a method for alleviating a pain state not associated with a cough condition by administration of a cyclooxygenase-2 inhibitor (also referred to as a cyclooxygenase II, COX-2 or COX II inhibitor), together with a centrally acting analgesic selected from the group consisting of a narcotic analgesic selected from the group consisting of codeine and hydrocodone; an agonist-antagonist analgesic and tramadol. This invention is also concerned with a method and composition therefor for treating pain by administering a cyclooxygenase-2 inhibitor together with a centrally acting analgesic selected from the group consisting of a narcotic analgesic other than codeine and hydrocodone; an agonist-antagonist analgesic and tramadol.

Recently, the gene for a second inducible form of cyclooxygenase, referred to as cyclooxygenase-2, has been cloned, sequenced and characterized initially from chicken, murine and human sources. Cyclooxygenase-2 is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. Cyclooxygenase-2 is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Therefore, a selective inhibitor of cyclooxygenase-2 can have similar antiinflammatory, analgesic and antipyretic properties to a conventional non-steroidal antiinflammatory drug (NSAID), and in addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects.

A number of cyclooxygenase-2 inhibitors are known. See, e.g., U.S. Patent Nos. 5,393,790; 5,409,944; 5,418,254; 5,420,343; 5,436,265; 5,466,823; 5,474,995; 5,476,944; 5,486,534; 5,510,368; 5,521,213; 5,536,752; 5,547,975; 5,550,142; 5,552,422; 5,565,482; 5,576,339; 5,580,985; 5,585,504; 5,593,994; 5,596,008; 5,604,253; 5,604,260; 5,639,780; 5,677,318; 5,691,374; 5,698,584; 5,710,140; 5,733,909; 5,767,291; 5,789,413 and 5,817,700. Cyclooxygenase-2 inhibitors exhibit a diminished ability to induce some of the mechanism-based side effects that occur with the use of NSAIDs. In particular, such inhibitors can have a reduced

potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a diminished ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

Narcotic analgesics such as codeine, dihydrocodeine, oxycodone, hydrocodone, meperidine, and propoxyphene are known and can produce tolerance and/or dependence. Each of U.S. Patent Nos. 5,409,944; 5,436,265; 5,474,995; 5,510,368; 5,521,213; 5,536,752; 5,550,142; 5,552,422; 5,604,253; 5,604,260; 5,639,780; 5,677,318; 5,691,374; 5,698,584; 5,710,140; 5,733,909; 5,767,291; 5,789,413 and 5,817,700 describe a composition containing a cyclooxygenase-2 inhibitor in combination with an opioid antitussive such as codeine or hydrocodone, or a nonopioid antiussive such as caramiphen, carbetapentane or dextromethorphan. However, none of these references even remotely suggest that the combination of a cyclooxygenase-2 inhibitor and an antitussive be used to treat pain which is not associated with a cough condition.

Agonist-antagonist analgesics are also known. In general, agonist-antagonist analgesics constitute a distinct subclass of opioids and are differentiated from the latter by their mixed actions, meaning, they are not full agonists at all opioid receptors, e.g., μ, δ, κ, etc. receptors. Instead, agonist-antagonists are believed to either exert their analgesic action by working as agonist analgesics at some opioid receptors and antagonists or very weak agonists at other opioid receptors, i.e., mixed agonist-antagonists, or exert their analgesic action by working as agonists at some opioid receptors, i.e., partial agonists. Mixed agonist-antagonist analgesics will typically be the combination of μ antagonism coupled with κ agonism. Partial agonist analgesics will typically be μ agonism.

The compound cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, commonly known as tramadol is an analgesic commercially available as the hydrochloride salt. The process by which tramadol may be made is described in U.S. Patent No. 3,652,589 the contents of which are incorporated herein by reference. Tramadol's analgesic effect is not derived from natural resources nor is it chemically related to opiates, e.g., morphine, codeine, hydrocone and oxycodone. A number of adverse side effects are associated with the administration of tramadol, e.g., dizziness, somnolence, nausea, constipation, sweating and pruritus, which are similar to that of an opioid. However, tramadol causes significantly less

respiratory depression than an opioid.

SUMMARY OF THE INVENTION

In accordance with the present invention, a method for alleviating a pain state not associated with a cough condition is provided which comprises administering to a mammal exhibiting a pain state not associated with a cough condition (a) at least one cyclooxygenase-2 inhibitor and (b) a centrally acting analgesic selected from the group consisting of a narcotic analgesic selected from the group consisting of codeine and hydrocodone; an agonist-antagonist analgesic and tramadol.

Further in accordance with the present invention, a method of alleviating pain is provided which comprises administering to a mammal exhibiting pain (a) at least one cyclooxygenase-2 inhibitor and (b) a centrally acting analgesic selected from the group consisting of a narcotic analgesic other than codeine and hydrocodone; an agonist-antagonist analgesic and tramadol.

Still further in accordance with this invention, a composition for alleviating pain is provided which comprises (a) at least one cycloxygenase-2 inhibitor and (b) a centrally acting analgesic selected from the group consisting of a narcotic analgesic other than codeine and hydrocodone; an agonist-antagonist analgesic; and tramadol.

The method of this invention and the analgesic composition therefor are applicable to the treatment of all varieties of pain, e.g., arthritic pain and other forms of chronic pain such as neuropathic pain, post-operative pain, lumbosacral pain, musculo-skeletal pain, headache, migraine, and the like, except in the case of an analgesic drug containing the narcotic analgesic codeine or hydrocodone where the pain states being treated is other than one accompanied by a cough condition.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Any of the cyclooxygenase-2 inhibitors heretofore used to alleviate pain can be used herein. Specific cyclooxygenase-2 inhibitors that can be used in this invention are disclosed in aforementioned U.S. Patent Nos. 5,393,790; 5,418,254; 5,420,343; 5,466,823; 5,476,944; 5,486,534; 5,547,975; 5,565,482; 5,576,339; 5,580,985; 5,585,504; 5,593,994; and 5,596,008, the contents of which are incorporated by reference herein. More particularly, the useful

cyclooxygenase-2 inhibitors include the substituted spiro compounds of U.S. Patent No. 5,393,790, e.g., 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene, 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide, 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene, and the like; the sulfonamides of U.S. Patent No. 5,409,944, e.g., 5-methanesulfonamido-6-(2-thienylthio)-1-indanone, 5-methanesulfonamido-6-(2-(4-methyl-1,3-diazinylthio))-1-indanone, 5-methanesulfonamido-6-(2-thiazolylthio)-1-indanone, and the like; the 2,3-substituted cyclopentadienyl compounds of U.S. Patent No. 5,418,254, e.g., 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene, 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide, 1-methylsulfonyl-4-{4-(4-trifluoromethylphenyl)-1-trifluoromethylcyclopenta-2,4-dien-3-yl]benzene, and the like; the aromatic cycloethers of U.S. Patent No. 5,420,343, e.g., methyl 3,5-bis(1,1-dimethylethyl)benzoate, 3,5-bis(1,1-dimethylethyl) benzenemethanol, 1,3-bis(1,1-dimethylethyl)-5-(2-chloroethyl)benzene, and the like; the 1-aroyl acids of U.S. Patent No. 5,436,265, e.g., 1-(2,4,6-trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid, 1-(2,6-dichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid and the like; the phenyl heterocycles of U.S. Patent Nos. 5,474,995, 5,536,752, 5,550,142, 5,710,140 and 5,767,291, e.g., 3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene, 2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopentenone, 4-(4-methylsulfonyl)phenyl)-5-(4-fluorophenyl)isothiazole, 4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene, 3-(4-(aminosulfonyl)phenyl)-2-4-(fluorophenyl)-5-(2-propyl)thiophene, 3-(4-(aminosulfonyl)phenyl)-2-cyclohexylthiophene, 3-(4-(aminosulfonyl)phenyl)-2-4-(fluorophenyl)-5-(2-hydroxy-2-propyl)thiophene, 3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene and the like; the benzenesulfonamides of U.S. Patent No. 5,466,823, e.g., 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (which is commonly referred to as celecoxib) and the like; the cyclic phenolic thioether derivatives of U.S. Patent No. 5,476,944, e.g., 3,5-bis(1,1-dimethylethyl)benzenethiol, trans-2-[[3,5-bis(1,1-dimethylethyl)henyl]hio]cyclohexanol, 3,6-dioxabicyclo-[3.1.0]hexane, and the like; the 3,4-substituted pyrazoles of U.S. Patent No. 5,486,534, e.g., 4-(4-fluorophenyl)-1-methyl-3-[4-(methylsulfonyl)phenyl]-5-trifluoromethyl)pyrazole, 1-benzyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)pyrazole, 1-allyl-4(4-fluorophenyl)-3-[4-methylsulfonyl)phenyl]-5-

(trifluoromethyl)-1H-pyrazole, and the like; the N-benzyl-3-indoleacetic acids of U.S. Patent No. 5,510,368, e.g., 2-(5-bromo-1-(4-bromobenzyl)-2-methyl-1H-indol-3-yl)propionic acid, (S)-(+)-2-(5-bromo-1-(4-bromophenyl)-2-methyl-1H-indol-3-yl)acetyl acid, (R)-(-)-2-(5-bromo-1-(4-bromobenzyl)-2-methyl-1H-indol-3-yl)propionic acid, and the like; the diaryl bicyclic heterocyclics of U.S. Patent No. 5,521,213, e.g., 3-(4-(methylsulfonyl)phenyl)-2-phenylbenzo[b]furan, 3-(4-(methanesulfonyl)phenyl)-2-phenylbenzo[b]thiophene, 2-(4-fluorophenyl)-3-(4-aminosulfonyl)phenyl)-4H-thieno[2,3-c]furan-6-one, and the like; the benzopyranopyrazolyl derivatives of U.S. Patent No. 5,547,975, e.g., 4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide, methyl[1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-[1]benzopyrano[4,3-c]pyrazol-3-yl] carboxylate, 4-[3-(trifluoromethyl)-1H-benzofuro[3,2-c]pyrazol-1-yl] benzenesulfonamide, and the like; the aryl substituted 5,5 fused aromatic nitrogen compounds of U.S. Patent No. 5,552,422, e.g., 5-(4-methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole, 2-methyl-5-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole, 3-methyl-5-(4-methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole, and the like; the heteroarylpyranopyrazolyl derivatives of U.S. Patent No. 5,565,482, e.g., 4-[1,5-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol, 4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano-[4,3-c]pyrazol-1-yl]benzenesulfonamide, 1,5-dihydro-6-fluoro-7-methoxy-1-[(4-methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano-[4,3-c]pyrazol-1-yl]benzenesulfonamide, and the like; the pyridyl substituted cyclopentadienes of U.S. Patent No. 5,576,339, e.g., 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene, 4-[4-(4-fluoropyhenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide, and the like; the substituted pyrazoles of U.S. Patent No. 5,580,985, e.g., 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole, 3-amino-4,4,4-trifluoro-2(4-fluorophenyl)-1-[4-(methylthio)phenyl]-2-buten-1-one, 1-benzyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)pyrazole, and the like; the lactones of U.S. Patent No. 5,585,504, e.g., 3-phenyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone, 3-(3,4-difluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, and the like; the ortho substituted phenyl compounds of U.S. Patent No. 5,593,994, e.g., 2-[(4-methylthio)phenyl]-1-biphenyl,1-cyclohexene-2-(4′-methylsulfonylphenyl) benzene, 3-(4′-methylsulfonylphenyl)-4-phenylphenol, and the like; the 3,4-diaryl substituted pyridines of U.S.

Patent No. 5,596,008, e.g., 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine, 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine, 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine, and the like; the N-benzylindol-3-yl propanoic acid derivatives of U.S. Patent No. 5,604,253, e.g., 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]propanoic acid, 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-2,2-dimethyl-propanoic acid, 2-Benzyl-3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]propanoic acid and the like; the 5-methanesulfonamido-1-indanones of U.S. Patent No. 5,604,260, e.g., 4-(2,4-Dichlorophenoxy)-3-nitrobenzaldehyde, 5-methanesulfonamido-6-(2,4-difluorophenylthio)-1-indanone and the like; the N-benzylindol-3-yl butanoic acid derivatives of U.S. Patent No. 5,639,780, e.g., [4-(1-(4-Bromobenzyl)-5-methoxy-2-methyl-1-H-indol-3-yl)-3-(ethane-1,2-diyl)]butanoic acid, 4-(1-(4-Bromobenzyl)-5-methoxy-2-methyl-1-H-indol-3-yl)-2-methylbutanoic acid and the like; the diphenyl-1,2-3-thiadiazoles of U.S. Patent No. 5,677,318, e.g., 4-Phenyl-5-(4-(methylsulfonyl)-phenyl-1,2,3-thiadiazole, 4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl-1,2,3-thiadiazole, 4-(3-fluorophenyl)-5-(4-(methylsulfonyl)phenyl-1,2,3-thiadiazole and the like; the diaryl-5-oxygenated-2-(5H)-furanones of U.S. Patent No. 5,691,374, e.g., 5-hydroxy-3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone, 5-hydroxy-5-methyl-,4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone, 5-hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone and the like; the 3,4-diaryl-2-hydroxy-2,5-dihydrofuranes of U.S. Patent No. 5,698,584, e.g., 3-(3,5-difluorophenyl)-5,5-dimethyl-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran, 5,5-dimethyl-3-(4-fluorophenyl)-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran, 5,5-dimethyl-2-ethoxy-3-(3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran and the like; the diphenyl stilbenes of U.S. Patent No. 5,733,909, e.g., (E)-3-(4-methylsulfonyl)phenyl-2-phenylbut-2-enoic acid methyl ester, (E)-3-(methylsulfonyl)phenyl-2-phenylbut-2-enoic acid, (E)-3-(4-methylsulfonyl)phenyl-1-morpholin-4-yl-2-phenylbut-2en-1-one and the like; the alkylated styrenes of U.S. Patent No. 5,789,413, e.g., 2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)-phenyl)-2-(Z)-penten-1.4-diol, acetic acid 4-acetoxy-2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-2-(Z)-pent-2-enyl ester, 2-(3-fluorophenyl)-4-methoxy-4-methyl-3-((4-methylsulfonyl1phenyl)-2-(Z)-pentenoic acid and the like; the bisaryl cyclobutene derivatives of U.S. Patent No. 5,817,700, e.g., 4,4-

dichloro-3-(4-methylthiophenyl)-2-phenyl-2-cyclobuten-1-one, 4,4-dichloro-3-(4-methylsulfonylphenyl)-2-phenyl-2-cyclobuten-1-one, 4-chloro-3-(4-methylsulfonylphenyl)-2-phenyl-2-cyclobuten-1-one and the like and MK-966 (which is also referred to by Merk & Co. as "VIOXX").

The second component of the drug composition of this invention is a centrally acting analgesic. Useful centrally acting analgesics for use herein include narcotic analgesics, agonist-antagonist analgesics and tramadol. When treating a pain state other than one accompained by a cough condition, the narcotic analgesics codeine, hydrocodone and their pharmaceutically acceptable salts can be used herein. Suitable narcotic analgesics for alleviating all pain states include morphine, heroin, hydromorphone, oxymorphine, levorphanol, levallorphan, methadone, merperidine, fentanyl, cocaine, oxycodone, propoxyphene, nalmefene, naloxone, naltrexone and their pharmaceutically acceptable salts with morphine, oxycodone and hydromorphone being more preferred.

Any of the agonist-antagonist analgesics heretofore used to alleviate pain can be used herein. For listings of agonist-antagonist analgesics, see e.g, Goodman and Gilman's "The Pharmaceutical Basis of Therapeutics", 8th ed., McGraw-Hill, Inc. (1990), pp. 510-514 and "Remingaton's Pharmaceutical Sciences", 17th ed., Mack Publishing Company (1985), pp. 1099-1110. Specific agonist-antagonist analgesics that can be used herein include pentazocine, pentazocine hydrochloride, nalbuphine, nalbuphine hydrochloride, butorphanol, butorphanol tartrate, buprenorphine, buprenorphine hydrochloride, maptazinol, dezocine, nalorphine, cyclazocine, their pharmaceutically acceptable salts and the like.

With respect to dosage levels, the cyclooxygenase-2 inhibitor and centrally acting analgesic must be present at a level corresponding to the generally recommended adult human dosages for a particular cyclooxygenase-2 inhibitor and centrally acting analgesic. Given the wide variation in dosage level of the cyclooxygenase-2 inhibitor which depends to a large extent on the specific cyclooxygenase-2 inhibitor being administered, there can similarly be a wide variation in the dosage level of the centrally acting analgesic which also depends on the specific centrally acting analgesic. These amounts can be determined for a particular drug combination in accordance with this invention employing routine experimental testing.

While the cyclooxygenase-2 inhibitor and centrally acting analgesic need not be

administered together, they must both be present in the patient at effective levels at the same time. While it is within the scope of the invention to separately administer the cyclooxygenase-2 inhibitor and centrally acting analgesic as a matter of convenience, it is preferred that these drugs be coadministered in a single dosage form. All modes of administrations are contemplated, e.g., orally, rectally, parenterally, topically, or by intravenous, intramuscular, intrastemal or subcutaneous injection or in a form suitable by inhalation. The formulations can, where appropriate, be conveniently presented in discrete dosage units and can be prepared by any of the methods well known in the art of pharmacy.

An analgesic composition containing the cyclooxygenase-2 inhibitor and centrally acting analgesic will ordinarily be formulated with one or more pharmaceutically acceptable ingredients in accordance with known and established practice. Thus, the composition can be formulated as a liquid, powder, elixir, injectable solution, etc. Formulations for oral use can be provided as tablets or hard capsules wherein the pharmacologically active ingredients are mixed with an inert solid diluent such as calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are mixed with water or miscible solvents such as proplyene glycol; PEG's and ethanol, or an oleaginous medium, e.g., peanut oil, liquid paraffin or olive oil.

For topical administration in the mouth, the compositions can take the form of buccal or sublingual tablet, drops or lozenges formulated in conventional manner.

For topical administration to the epidermis the compounds of the invention can be formulated as creams, gels, ointments or lotions or as transdermal patches. Such compositions can, for example, be formulated with an aqueous or oily base with the addition of suitable thickening, gelling, emulsifying, stabilizing, dispersing, suspending and/or coloring agents.

The compounds of the invention can also be formulated as depot preparations. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example as a sparingly soluble salt.

The compounds of the invention can be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by

bolus injection or continuous intravenous infusion. Formulations for injection can be presented in unit dosage from e.g. in ampoules or in multi-does containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention can also be formulated in rectal compositions such as suppositories or retention enemas e.g. containing conventional suppository bases such as cocoa butter or other gylceride.

For intranasal administration, the compounds of the invention can be used, for example, as a liquid spray, as a powder or in the form of drops.

For administration by inhalation, the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insulator can be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Aqueous suspensions can include pharmaceutically acceptable excipients such as suspending agents, e.g., sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as naturally occurring phosphatide, e.g., lecithin, or condensation products of an alkylene oxide with fatty acids, e.g., polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, eg., heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, e.g., polyoxyethylene sorbitol monoleate or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, e.g., polyoxyethylene sorbitan monoleate. The aqueous suspensions can also contain one or more preservatives, e.g., ehtyl-or-n-proply-p-hydroxy benzoate, one or more coloring agents, one

or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin or sodium or calcium cyclamate.

The cyclooxygenase-2 inhibitor and centrally acting analgesic can also be administered with at least one other pharmacologically active substance, e.g., a non-narcotic analgesic such as acetaminophen, aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolemtin, zomepirac, and the like.

EXAMPLES 1-35

The following unit dosage forms are illustrative of the pain-alleviating drug combinations in accordance with the present invention:

Example	Cyclooxygenase-2 Inhibitor (mg)	Centrally Acting Analagesic (mg)	Additional Active Component (mg)
1	5-(4-fluorophenyl)-6-[4-(methyl-sulfonyl)phenyl]spiro[2.4]hept-5-ene (25)	morphine (35)	
2	5-(4-fluorophenyl)-6-[4-(methyl-sulfonyl)phenyl]spiro[2.4]hept-5-ene (25)	pentazocine (35)	acetaminophen (325)
3	5-(4-fluorophenyl)-6-[4-(methyl-sulfonyl)phenyl]spiro[2.4]hept-5-ene (25)	tramadol (50)	
4	5-methanesulfonamido-6-(2-thienylthio)-1-indanone(25)	oxycodone (35)	
5	5-methanesulfonamido-6-(2-thienylthio)-1-indanone(25)	nalbuphine (35)	acetaminophen (325)
6	5-methanesulfonamido-6-(2-thienylthio)-1-indanone(25)	tramadol (50)	
7	5-methanesulfonamido-6-(2-thienylthio)-1-indanone(25)	morphine (30) nalbuphine (30)	
8	5-methanesulfonamido-6-(2-thienylthio)-1-indanone(25)	morphine (30) tramadol (40)	
9	methyl 3,5-bis(1,1-dimethylethyl) benzoate (25)	hydromorphone (35)	
10	methyl 3,5-bis(1,1-dimethylethyl) benzoate (25)	butorphanol (35)	acetaminophen (325)

Centrally Acting Additional Active

Example	Cyclooxygenase-2 Inhibitor (mg)	Analagesic (mg)	Component (mg)
11	methyl 3,5-bis(1,1-dimethylethyl) benzoate (25)	tramadol (75)	
12	methyl 3,5-bis(1,1-dimethylethyl) benzoate (25)	oxycodone (30) butorphanol (30)	
13	methyl 3,5-bis(1,1-dimethylethyl) benzoate (25)	butorphanol (30) tramadol (40)	
14	1-(2,4,6-trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid (25)	morphine (35)	
15	1-(2,4,6-trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid (25)	buprenorphine (35)	ibuprofen (325)
16	1-(2,4,6-trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid (25)	morphine (35)	
17	1-(2,4,6-trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid (25)	meptazinol (35)	
18	1-(2,4,6-trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid (25)	tramadol (30)	
19	3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene (30)	oxycodone (35)	
20	3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene (30)	dezocine (25)	aspirin (325)
21	3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene (30)	tramadol (50)	
22	3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene (30)	oxycodone (35) dezocine (30)	
23	3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene (30)	dezocine (30) tramadol (40)	
24	3,5-bis(1,1-dimethylethyl)benzenethiol (25)	hydromorphone (35)	
25	3,5-bis(1,1-dimethylethyl)benzenethiol (25)	nalorphine (35)	acetaminophen (325)
26	3,5-bis(1,1-dimethylethyl)benzenethiol (25)	tramadol (50)	
27	3,5-bis(1,1-dimethylethyl)benzenethiol (25)	cyclazocine (30)	
28	3,5-bis(1,1-dimethylethyl)benzenethiol (25)	morphine (30)	
29	3-(4-(methylsulfonyl)phenyl)-2-phenylbenzo [b]furan (25)	nalbuphine (35)	
30	3-(4-(methylsulfonyl)phenyl)-2-phenylbenzo [b]furan (25)	dezocine (35)	ibuprofen (325)
31	3-(4-(methylsulfonyl)phenyl)-2-phenylbenzo [b]furan (25)	oxycodone (35)	

Example	Cyclooxygenase-2 Inhibitor (mg)	Centrally Acting Analagesic (mg)	Additional Active Component (mg)
32	4-[1,4-dihydro-3-(trifluoromethyl)-[1] benzopyrano[4,3-c]pyrazol-1-yl] benzenesulfonamide (25)	morphine (35) butorphanol (30) tramadol (30)	
33	5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo [2,1-b]thiazol (25)	morphine (35)	
34	4-[1,5-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c] pyrazol-1-yl]benzenesulfonamide (25)	codeine (35)	
35	1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-diene-3-yl] benzene (25)	hydrocodone (30)	

In each of the dosage units, the cyclooxygenase -2 inhibitor and centrally acting analgesic significantly alleviate pain.

WHAT IS CLAIMED IS

1. A method of alleviating a pain state not associated with a cough condition which comprises administering to a mammal exhibiting a pain state not associated with a cough condition (a) at least one cyclooxygenase-2 inhibitor and (b) a centrally acting analgesic selected from the group consisting of a narcotic analgesic selected from the group consisting of codeine, hydrocodone and pharmaceutically acceptable salts thereof; an agonist-antagonist analgesic and tramadol.

2. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is selected from the group consisting of substituted spiro compound, sulfonamide, 2,3-substituted cyclopentadienyl compound, aromatic cycloether, 1-aroyl acid, phenyl heterocycle, benzenesulfonamide, cyclic phenolic thioether derivative, 3,4-substituted pyrazole, N-benzyl-3-indoleacetic acid, diaryl bicyclic heterocyclic, benzopyranopyrazolyl derivative, aryl substituted 5,5 fused aromatic nitrogen compound, heteroarylpyranopyrazolyl derivative, pyridyl substituted cyclopentadiene, substituted pyrazole, lactone, ortho substituted phenyl compound, 3,4-diaryl substituted pyridine, N-benzylindol-3-yl propanoic acid derivatives, 5-methanesulfonamido-1-indanones, N-benzylindol-3-yl butanoic acid derivatives, diphenyl-1,2-3-thiadiazoles, diaryl-5-oxygenated-2-(5H)-furanones, 3,4-diaryl-2-hydroxy-2,5-dihydrofuranes, diphenyl stilbenes, bisaryl cyclobutene derivatives and MK-966.

3. The method of Claim 2 wherein the substituted spiro compound is selected from the group consisting of 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene, 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide and 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl] spiro[3.4]oct-6-ene, sulfonamides is selected form the group consisting of 5-methanesulfonamido-6-(2-thienylthio)-1-indanone and 5-methanesulfonamido-6-(2-(4-methyl-1,3-diazinylthio))-1-indanone, 5-methanesulfonamido-6-(2-thiazolylthio)-1-indanone, the 2,3-substituted cyclopentadienyl compound is selected from the group consisting of 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene, 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide and 1-methylsulfonyl-4-{4-(4-trifluoromethylphenyl)-1-

trifluoromethylcyclopenta-2,4-dien-3-yl]benzene, the aromatic cycloether is selected from the group consisting of methyl 3,5-bis(1,1-dimethylethyl)benzoate, 3,5-bis(1,1-dimethylethyl) benzenemethanol and 1,3-bis(1,1-dimethylethyl)-5-(2-chloroethyl)benzene, the 1-aroyl acid is selected from the group consisting of 1-(2,4,6-trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid and 1-(2,6-dichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid, the phenyl heterocycle is selected from the group consisting of 3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene, 2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopentenone, 4-(4-methylsulfonyl)phenyl)-5-(4-fluorophenyl)isothiazole, 4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene, 3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)-5-(2-propyl)thiophene, 3-(4-(aminosulfonyl)phenyl)-2-cyclohexylthiophene, 3-(4-(aminosulfonyl)phenyl)-2-4-(fluorophenyl)-5-(2-hydroxy-2-propyl)thiophene and 3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene, the benzenesulfonamide which is 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide, the cyclic phenolic thioether derivative is selected from the group consisting of 3,5-bis(1,1-dimethylethyl)benzenethiol, trans-2-[[3,5-bis(1,1-dimethylethyl)henyl] hio]cyclohexanol and 3,6-dioxabicyclo-[3.1.0]hexane, the 3,4-substituted pyrazole is selected from the group consisting of 4-(4-fluorophenyl)-1-methyl-3-[4-(methylsulfonyl)phenyl]-5-trifluoromethyl)pyrazole, 1-benzyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)pyrazole and 1-allyl-4(4-fluorophenyl)-3-[4-methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole, the N-benzyl-3-indoleacetic acid is selected from the group consisting of 2-(5-bromo-1-(4-bromobenzyl)-2-methyl-1H-indol-3-yl)propionic acid, (S)-(+)-2-(5-bromo-1-(4-bromophenyl)-2-methyl-1H-indol-3-yl)acetyl acid and (R)-(-)-2-(5-bromo-1-(4-bromobenzyl)-2-methyl-1H-indol-3-yl)propionic acid, the diaryl bicyclic heterocyclic is selected from the group consisting of 3-(4-(methylsulfonyl)phenyl)-2-phenylbenzo[b]furan, 3-(4-(methanesulfonyl)phenyl)-2-phenylbenzo[b]thiophene and 2-(4-fluorophenyl)-3-(4-aminosulfonyl)phenyl)-4H-thieno[2,3-c]furan-6-one, the benzopyranopyrazolyl derivative is selected from the group consisting of 4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide, methyl[1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-

[1]benzopyrano[4,3-c]pyrazol-3-yl] carboxylate and 4-[3-(trifluoromethyl)-1H-benzofuro[3,2-c]pyrazol-1-yl] benzenesulfonamide, the aryl substituted 5,5 fused aromatic nitrogen compound is selected from the group consisting of 5-(4-methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole, 2-methyl-5-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole and 3-methyl-5-(4-methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole, the heteroarylpyranopyrazolyl derivative is selected from the group consisting of 4-[1,5-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol, 4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano-[4,3-c]pyrazol-1-yl]benzenesulfonamide and 1,5-dihydro-6-fluoro-7-methoxy-1-[(4-methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano-[4,3-c]pyrazol-1-yl]benzenesulfonamide, the pyridyl substituted cyclopentadienes is selected from the group consisting of 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene and 4-[4-(4-fluoropyhenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide, the substituted pyrazole is selected from the group consisting of 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole, 3-amino-4,4,4-trifluoro-2(4-fluorophenyl)-1-[4-(methylthio)phenyl]-2-buten-1-one and 1-benzyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)pyrazole, the lactone is selected from the group consisting of 3-phenyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone and 3-(3,4-difluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, the ortho substituted phenyl compound is selected from the group consisting of 2-[(4-methylthio)phenyl]-1-biphenyl,1-cyclohexene-2-(4′-methylsulfonylphenyl) benzene, and 3-(4′-methylsulfonylphenyl)-4-phenylphenol, the 3,4-diaryl substituted pyridine is selected from the group consisting of 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine, 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine and 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine, the N-benzylindol-3-yl propanoic acid derivatives selected from the group consisting of 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]propanoic acid, 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-2,2-dimethyl-propanoic acid and 2-Benzyl-3-[1-(p-

Bromobenzyl)-5-methoxy-2-methylindol-3-yl]propanoic acid, the 5-methanesulfonamido-1-indanones selected from the group consisting of 4-(2,4-Dichlorophenoxy)-3-nitrobenzaldehyde and 5-methanesulfonamido-6-(2,4-difluorophenylthio)-1-indanone, the N-benzylindol-3-yl butanoic acid derivatives selected from the group consisting of [4-(1-(4-Bromobenzyl)-5-methoxy-2-methyl-1-H-indol-3-yl)-3-(ethane-1,2-diyl)]butanoic acid and 4-(1-(4-Bromobenzyl)-5-methoxy-2-methyl-1-H-indol-3-yl)-2-methylbutanoic acid, the diphenyl-1,2-3-thiadiazoles selected from the group consisting of 4-Phenyl-5-(4-(methylsulfonyl)-phenyl-1,2,3-thiadiazole, 4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl-1,2,3-thiadiazole and 4-(3-fluorophenyl)-5-(4-(methylsulfonyl)phenyl-1,2,3-thiadiazole, the diaryl-5-oxygenated-2-(5H)-furanones selected from the group consisting of 5-hydroxy-3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone, 5-hydroxy-5-methyl-,4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone and 5-hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone, the 3,4-diaryl-2-hydroxy-2,5-dihydrofuranes selected from the group consisting of 3-(3,5-difluorophenyl)-5,5-dimethyl-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran, 5,5-dimethyl-3-(4-fluorophenyl)-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran and 5,5-dimethyl-2-ethoxy-3-(3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran, the diphenyl stilbenes selected from the group consisting of (E)-3-(4-methylsulfonyl)phenyl-2-phenylbut-2-enoic acid methyl ester, (E)-3-(methylsulfonyl)phenyl-2-phenylbut-2-enoic acid and (E)-3-(4-methylsulfonyl)phenyl-1-morpholin-4-yl-2-phenylbut-2en-1-one, the alkylated styrenes selected from the group consisting of 2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)-phenyl)-2-(Z)-penten-1.4-diol, acetic acid 4-acetoxy-2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-2-(Z)-pent-2-enyl ester and 2-(3-fluorophenyl)-4-methoxy-4-methyl-3-((4-methylsulfonyl1phenyl)-2-(Z)-pentenoic acid, and the bisaryl cyclobutene derivatives selected from the group consisting of 4,4-dichloro-3-(4-methylthiophenyl)-2-phenyl-2-cyclobuten-1-one, 4,4-dichloro-3-(4-methylsulfonylphenyl)-2-phenyl-2-cyclobuten-1-one and 4-chloro-3-(4-methylsulfonylphenyl)-2-phenyl-2-cyclobuten-1-one.

4. The method of Claim 1 wherein the agonist-antagonist analgesic is selected from the group consisting of pentazocine, nalbuphine, butorphanol, buprenorphine, meptazinol, dezocine, nalorphine, cyclazocine and pharmaceutically acceptable salts thereof.

5. The method of Claim 1 containing a therapeutically effective amount of at least one other pharmacologically active substance (c).

6. The method of Claim 5 wherein the pharmacologically active substanct (c) is a non-narcotic analgesic.

7. The method of Claim 6 wherein the non-narcotic analgesic is selected from the group consisting of acetaminophen, aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, ppiroxicam, sulindac, tolmetin and zomepirac.

8. The method of Claim 1 wherein (a) and (b) are coadministered.

9. The method of Claim 1 wherein the pain being treated or to be treated is chronic pain, post-operative pain, lumbosacral pain, musculo-skeletal pain, headache or migraine.

10. A method of alleviating pain which comprises administering to a mammal exhibiting pain (a) at least one cyclooxygenase-2 inhibitor and (b) a centrally acting analgesic selected from the group consisting of a narcotic analgesic other than codeine and hydrocodone; an agonist-antagonist analgesic and tramadol.

11. The method of Claim 10 wherein the cyclooxygenase-2 inhibitor is selected from the group consisting of substituted spiro compound, sulfonamide, 2,3-substituted cyclopentadienyl compound, aromatic cycloether, 1-aroyl acid, phenyl heterocycle, benzenesulfonamide, cyclic phenolic thioether derivative, 3,4-substituted pyrazole, N-benzyl-3-indoleacetic acid, diaryl bicyclic heterocyclic, benzopyranopyrazolyl derivative, aryl substituted 5,5 fused aromatic nitrogen compound, heteroarylpyranopyrazolyl derivative, pyridyl substituted cyclopentadiene, substituted pyrazole, lactone, ortho substituted phenyl compound, 3,4-diaryl substituted pyridine, N-benzylindol-3-yl propanoic acid derivatives, 5-methanesulfonamido-1-indanones, N-benzylindol-3-yl

butanoic acid derivatives, diphenyl-1,2-3-thiadiazoles, diaryl-5-oxygenated-2-(5H)-furanones, 3,4-diaryl-2-hydroxy-2,5-dihydrofuranes, diphenyl stilbenes, bisaryl cyclobutene derivatives and MK-966.

12. The method of Claim 11 wherein the substituted spiro compound is selected from the group consisting of 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene, 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide and 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl] spiro[3.4]oct-6-ene, sulfonamides is selected form the group consisting of 5-methanesulfonamido-6-(2-thienylthio)-1-indanone and 5-methanesulfonamido-6-(2-(4-methyl-1,3-diazinylthio))-1-indanone, 5-methanesulfonamido-6-(2-thiazolylthio)-1-indanone, the 2,3-substituted cyclopentadienyl compound is selected from the group consisting of 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene, 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide and 1-methylsulfonyl-4-{4-(4-trifluoromethylphenyl)-1-trifluoromethylcyclopenta-2,4-dien-3-yl]benzene, the aromatic cycloether is selected from the group consisting of methyl 3,5-bis(1,1-dimethylethyl)benzoate, 3,5-bis(1,1-dimethylethyl) benzenemethanol and 1,3-bis(1,1-dimethylethyl)-5-(2-chloroethyl)benzene, the 1-aroyl acid is selected from the group consisting of 1-(2,4,6-trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid and 1-(2,6-dichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid, the phenyl heterocycle is selected from the group consisting of 3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene, 2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopentenone, 4-(4-methylsulfonyl)phenyl)-5-(4-fluorophenyl)isothiazole, 4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene, 3-(4-(aminosulfonyl)phenyl)-2-4-fluorophenyl)-5-(2-propyl)thiophene, 3-(4-(aminosulfonyl)phenyl)-2-cyclohexylthiophene, 3-(4-(aminosulfonyl)phenyl)-2-4-(fluorophenyl)-5-(2-hydroxy-2-propyl)thiophene and 3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene, the benzenesulfonamide which is 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide, the cyclic phenolic thioether derivative is selected from the group consisting of 3,5-bis(1,1-dimethylethyl)benzenethiol, trans-2-[[3,5-bis(1,1-dimethylethyl)henyl] hio]cyclohexanol

and 3,6-dioxabicyclo-[3.1.0]hexane, the 3,4-substituted pyrazole is selected from the group consisting of 4-(4-fluorophenyl)-1-methyl-3-[4-(methylsulfonyl)phenyl]-5-trifluoromethyl)pyrazole, 1-benzyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)pyrazole and 1-allyl-4(4-fluorophenyl)-3-[4-methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole, the N-benzyl-3-indoleacetic acid is selected from the group consisting of 2-(5-bromo-1-(4-bromobenzyl)-2-methyl-1H-indol-3-yl)propionic acid, (S)-(+)-2-(5-bromo-1-(4-bromophenyl)-2-methyl-1H-indol-3-yl)acetyl acid and (R)-(-)-2-(5-bromo-1-(4-bromobenzyl)-2-methyl-1H-indol-3-yl)propionic acid, the diaryl bicyclic heterocyclic is selected from the group consisting of 3-(4-(methylsulfonyl)phenyl)-2-phenylbenzo[b]furan, 3-(4-(methanesulfonyl)phenyl)-2-phenylbenzo[b]thiophene and 2-(4-fluorophenyl)-3-(4-aminosulfonyl)phenyl)-4H-thieno[2,3-c]furan-6-one, the benzopyranopyrazolyl derivative is selected from the group consisting of 4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide, methyl[1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-[1]benzopyrano[4,3-c]pyrazol-3-yl] carboxylate and 4-[3-(trifluoromethyl)-1H-benzofuro[3,2-c]pyrazol-1-yl] benzenesulfonamide, the aryl substituted 5,5 fused aromatic nitrogen compound is selected from the group consisting of 5-(4-methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole, 2-methyl-5-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole and 3-methyl-5-(4-methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole, the heteroarylpyranopyrazolyl derivative is selected from the group consisting of 4-[1,5-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol, 4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano-[4,3-c]pyrazol-1-yl]benzenesulfonamide and 1,5-dihydro-6-fluoro-7-methoxy-1-[(4-methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano-[4,3-c]pyrazol-1-yl]benzenesulfonamide, the pyridyl substituted cyclopentadienes is selected from the group consisting of 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene and 4-[4-(4-fluoropyhenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide, the substituted pyrazole is selected from the group consisting of 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole, 3-amino-4,4,4-trifluoro-2(4-

fluorophenyl)-1-[4-(methylthio)phenyl]-2-buten-1-one and 1-benzyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)pyrazole, the lactone is selected from the group consisting of 3-phenyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone and 3-(3,4-difluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, the ortho substituted phenyl compound is selected from the group consisting of 2-[(4-methylthio)phenyl]-1-biphenyl,1-cyclohexene-2-(4′-methylsulfonylphenyl) benzene, and 3-(4′-methylsulfonylphenyl)-4-phenylphenol, the 3,4-diaryl substituted pyridine is selected from the group consisting of 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine, 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine and 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine, the N-benzylindol-3-yl propanoic acid derivatives selected from the group consisting of 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]propanoic acid, 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-2,2-dimethyl-propanoic acid and 2-Benzyl-3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]propanoic acid, the 5-methanesulfonamido-1-indanones selected from the group consisting of 4-(2,4-Dichlorophenoxy)-3-nitrobenzaldehyde and 5-methanesulfonamido-6-(2,4-difluorophenylthio)-1-indanone, the N-benzylindol-3-yl butanoic acid derivatives selected from the group consisting of [4-(1-(4-Bromobenzyl)-5-methoxy-2-methyl-1-H-indol-3-yl)-3-(ethane-1,2-diyl)]butanoic acid and 4-(1-(4-Bromobenzyl)-5-methoxy-2-methyl-1-H-indol-3-yl)-2-methylbutanoic acid, the diphenyl-1,2-3-thiadiazoles selected from the group consisting of 4-Phenyl-5-(4-(methylsulfonyl)-phenyl-1,2,3-thiadiazole, 4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl-1,2,3-thiadiazole and 4-(3-fluorophenyl)-5-(4-(methylsulfonyl)phenyl-1,2,3-thiadiazole, the diaryl-5-oxygenated-2-(5H)-furanones selected from the group consisting of 5-hydroxy-3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone, 5-hydroxy-5-methyl-,4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone and 5-hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone, the 3,4-diaryl-2-hydroxy-2,5-dihydrofuranes selected from the group consisting of 3-(3,5-difluorophenyl)-5,5-dimethyl-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran, 5,5-dimethyl-3-(4-

fluorophenyl)-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran and 5,5-dimethyl-2-ethoxy-3-(3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran, the diphenyl stilbenes selected from the group consisting of (E)-3-(4-methylsulfonyl)phenyl-2-phenylbut-2-enoic acid methyl ester, (E)-3-(methylsulfonyl)phenyl-2-phenylbut-2-enoic acid and (E)-3-(4-methylsulfonyl)phenyl-1-morpholin-4-yl-2-phenylbut-2en-1-one, the alkylated styrenes selected from the group consisting of 2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)-phenyl)-2-(Z)-penten-1.4-diol, acetic acid 4-acetoxy-2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-2-(Z)-pent-2-enyl ester and 2-(3-fluorophenyl)-4-methoxy-4-methyl-3-((4-methylsulfonyl1phenyl)-2-(Z)-pentenoic acid, and the bisaryl cyclobutene derivatives selected from the group consisting of 4,4-dichloro-3-(4-methylthiophenyl)-2-phenyl-2-cyclobuten-1-one, 4,4-dichloro-3-(4-methylsulfonylphenyl)-2-phenyl-2-cyclobuten-1-one and 4-chloro-3-(4-methylsulfonylphenyl)-2-phenyl-2-cyclobuten-1-one.

13. The method of Claim 10 wherein the narcotic analgesic is selected from the group consisting of morphine, oxycodone, hydromorphone and pharmaceutically acceptable salts thereof.

14. The method of Claim 10 wherein the agonist-antagonist analgesic is selected from the group consisting of pentazocine, nalbuphine, butorphanol, buprenorphine, meptazinol, dezocine, nalorphine, cyclazocine and pharmaceutically acceptable salts thereof.

15. The method of Claim 10 containing a therapeutically effective amount of at least one other pharmacologically active substance (c).

16. The method of Claim 15 wherein the pharmacologically active substanct (c) is a non-narcotic analgesic.

17. The method of Claim 16 wherein the non-narcotic analgesic is selected from the group consisting of acetaminophen, aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, ppiroxicam, sulindac, tolmetin and zomepirac.

18. The method of Claim 1 wherein (a) and (b) are coadministered.

19. The method of Claim 10 wherein the pain being treated or to be treated is chronic pain, post-operative pain, lumbosacral pain, musculo-skeletal pain, headache or migraine.

20. An analgesic composition comprising (a) at least one cyclooxygenase-2 inhibitor and (b) a centrally acting analgesic selected from the group consisting of a narcotic analgesic other than codeine and hydrocodone; an agonist-antagonist analgesic and tramadol.

21. The analgesic composition of Claim 20 wherein the cyclooxygenase-2 inhibitor is selected from the group consisting of substituted spiro compound, sulfonamide, 2,3-substituted cyclopentadienyl compound, aromatic cycloether, 1-aroyl acid, phenyl heterocycle, benzenesulfonamide, cyclic phenolic thioether derivative, 3,4-substituted pyrazole, N-benzyl-3-indoleacetic acid, diaryl bicyclic heterocyclic, benzopyranopyrazolyl derivative, aryl substituted 5,5 fused aromatic nitrogen compound, heteroarylpyranopyrazolyl derivative, pyridyl substituted cyclopentadiene, substituted pyrazole, lactone, ortho substituted phenyl compound, 3,4-diaryl substituted pyridine, N-benzylindol-3-yl propanoic acid derivatives, 5-methanesulfonamido-1-indanones, N-benzylindol-3-yl butanoic acid derivatives, diphenyl-1,2-3-thiadiazoles, diaryl-5-oxygenated-2-(5H)-furanones, 3,4-diaryl-2-hydroxy-2,5-dihydrofuranes, diphenyl stilbenes, bisaryl cyclobutene derivatives and MK-966.

22. The analgesic composition of Claim 21 wherein the substituted spiro compound is selected from the group consisting of 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene, 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide and 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl] spiro[3.4]oct-6-ene, sulfonamides is selected form the group consisting of 5-methanesulfonamido-6-(2-thienylthio)-1-indanone and 5-methanesulfonamido-6-(2-(4-methyl-1,3-diazinylthio))-1-indanone, 5-methanesulfonamido-6-(2-thiazolylthio)-1-indanone, the 2,3-substituted cyclopentadienyl compound is selected from the group consisting of 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene, 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide and 1-methylsulfonyl-4-{4-(4-trifluoromethylphenyl)-1-

trifluoromethylcyclopenta-2,4-dien-3-yl]benzene, the aromatic cycloether is selected from the group consisting of methyl 3,5-bis(1,1-dimethylethyl)benzoate, 3,5-bis(1,1-dimethylethyl) benzenemethanol and 1,3-bis(1,1-dimethylethyl)-5-(2-chloroethyl)benzene, the 1-aroyl acid is selected from the group consisting of 1-(2,4,6-trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid and 1-(2,6-dichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid, the phenyl heterocycle is selected from the group consisting of 3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene, 2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopentenone, 4-(4-methylsulfonyl)phenyl)-5-(4-fluorophenyl)isothiazole, 4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene, 3-(4-(aminosulfonyl)phenyl)-2-4-fluorophenyl)-5-(2-propyl)thiophene, 3-(4-(aminosulfonyl)phenyl)-2-cyclohexylthiophene, 3-(4-(aminosulfonyl)phenyl)-2-4-(fluorophenyl)-5-(2-hydroxy-2-propyl)thiophene and 3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene, the benzenesulfonamide which is 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide, the cyclic phenolic thioether derivative is selected from the group consisting of 3,5-bis(1,1-dimethylethyl)benzenethiol, trans-2-[[3,5-bis(1,1-dimethylethyl)henyl] hio]cyclohexanol and 3,6-dioxabicyclo-[3.1.0]hexane, the 3,4-substituted pyrazole is selected from the group consisting of 4-(4-fluorophenyl)-1-methyl-3-[4-(methylsulfonyl)phenyl]-5-trifluoromethyl)pyrazole, 1-benzyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)pyrazole and 1-allyl-4(4-fluorophenyl)-3-[4-methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole, the N-benzyl-3-indoleacetic acid is selected from the group consisting of 2-(5-bromo-1-(4-bromobenzyl)-2-methyl-1H-indol-3-yl)propionic acid, (S)-(+)-2-(5-bromo-1-(4-bromophenyl)-2-methyl-1H-indol-3-yl)acetyl acid and (R)-(-)-2-(5-bromo-1-(4-bromobenzyl)-2-methyl-1H-indol-3-yl)propionic acid, the diaryl bicyclic heterocyclic is selected from the group consisting of 3-(4-(methylsulfonyl)phenyl)-2-phenylbenzo[b]furan, 3-(4-(methanesulfonyl)phenyl)-2-phenylbenzo[b]thiophene and 2-(4-fluorophenyl)-3-(4-aminosulfonyl)phenyl)-4H-thieno[2,3-c]furan-6-one, the benzopyranopyrazolyl derivative is selected from the group consisting of 4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano[4,3-c]pyrazol-1-yl]benzenesulfonamide, methyl[1-[4-(aminosulfonyl)phenyl]-1,4-dihydro-

[1]benzopyrano[4,3-c]pyrazol-3-yl] carboxylate and 4-[3-(trifluoromethyl)-1H-benzofuro[3,2-c]pyrazol-1-yl] benzenesulfonamide, the aryl substituted 5,5 fused aromatic nitrogen compound is selected from the group consisting of 5-(4-methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole, 2-methyl-5-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole and 3-methyl-5-(4-methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole, the heteroarylpyranopyrazolyl derivative is selected from the group consisting of 4-[1,5-dihydro-6-fluoro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol, 4-[1,4-dihydro-3-(trifluoromethyl)-[1]benzopyrano-[4,3-c]pyrazol-1-yl]benzenesulfonamide and 1,5-dihydro-6-fluoro-7-methoxy-1-[(4-methylsulfonyl)phenyl]-3-(trifluoromethyl)-[2]benzothiopyrano-[4,3-c]pyrazol-1-yl]benzenesulfonamide, the pyridyl substituted cyclopentadienes is selected from the group consisting of 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene and 4-[4-(4-fluoropyhenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide, the substituted pyrazole is selected from the group consisting of 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole, 3-amino-4,4,4-trifluoro-2(4-fluorophenyl)-1-[4-(methylthio)phenyl]-2-buten-1-one and 1-benzyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)pyrazole, the lactone is selected from the group consisting of 3-phenyl-4-(4-methylsulfonyl)phenyl-2-(5H)-furanone and 3-(3,4-difluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, the ortho substituted phenyl compound is selected from the group consisting of 2-[(4-methylthio)phenyl]-1-biphenyl,1-cyclohexene-2-(4′-methylsulfonylphenyl) benzene, and 3-(4′-methylsulfonylphenyl)-4-phenylphenol, the 3,4-diaryl substituted pyridine is selected from the group consisting of 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine, 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine and 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine, the N-benzylindol-3-yl propanoic acid derivatives selected from the group consisting of 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]propanoic acid, 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-2,2-dimethyl-propanoic acid and 2-Benzyl-3-[1-(p-

Bromobenzyl)-5-methoxy-2-methylindol-3-yl]propanoic acid, the 5-methanesulfonamido-1-indanones selected from the group consisting of 4-(2,4-Dichlorophenoxy)-3-nitrobenzaldehyde and 5-methanesulfonamido-6-(2,4-difluorophenylthio)-1-indanone, the N-benzylindol-3-yl butanoic acid derivatives selected from the group consisting of [4-(1-(4-Bromobenzyl)-5-methoxy-2-methyl-1-H-indol-3-yl)-3-(ethane-1,2-diyl)]butanoic acid and 4-(1-(4-Bromobenzyl)-5-methoxy-2-methyl-1-H-indol-3-yl)-2-methylbutanoic acid, the diphenyl-1,2-3-thiadiazoles selected from the group consisting of 4-Phenyl-5-(4-(methylsulfonyl)-phenyl-1,2,3-thiadiazole, 4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl-1,2,3-thiadiazole and 4-(3-fluorophenyl)-5-(4-(methylsulfonyl)phenyl-1,2,3-thiadiazole, the diaryl-5-oxygenated-2-(5H)-furanones selected from the group consisting of 5-hydroxy-3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone, 5-hydroxy-5-methyl-,4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone and 5-hydroxy-4-(4-(methylsulfonyl)phenyl)-3-phenyl-2-(5H)-furanone, the 3,4-diaryl-2-hydroxy-2,5-dihydrofuranes selected from the group consisting of 3-(3,5-difluorophenyl)-5,5-dimethyl-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran, 5,5-dimethyl-3-(4-fluorophenyl)-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran and 5,5-dimethyl-2-ethoxy-3-(3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran, the diphenyl stilbenes selected from the group consisting of (E)-3-(4-methylsulfonyl)phenyl-2-phenylbut-2-enoic acid methyl ester, (E)-3-(methylsulfonyl)phenyl-2-phenylbut-2-enoic acid and (E)-3-(4-methylsulfonyl)phenyl-1-morpholin-4-yl-2-phenylbut-2en-1-one, the alkylated styrenes selected from the group consisting of 2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)-phenyl)-2-(Z)-penten-1.4-diol, acetic acid 4-acetoxy-2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-2-(Z)-pent-2-enyl ester and 2-(3-fluorophenyl)-4-methoxy-4-methyl-3-((4-methylsulfonyl1phenyl)-2-(Z)-pentenoic acid, and the bisaryl cyclobutene derivatives selected from the group consisting of 4,4-dichloro-3-(4-methylthiophenyl)-2-phenyl-2-cyclobuten-1-one, 4,4-dichloro-3-(4-methylsulfonylphenyl)-2-phenyl-2-cyclobuten-1-one and 4-chloro-3-(4-methylsulfonylphenyl)-2-phenyl-2-cyclobuten-1-one.

23. The analgesic composition of Claim 20 wherein the narcotic analgesic is selected from the group consisting of morphine, oxycodone, hydromorphone and pharmaceutially acceptable salts thereof.

24. The analgesic composition of Claim 20 wherein the agonist-antagonist analgesic is selected from the group consisting of pentazocine, nalbuphine, butorphanol, buprenophine, meptazinol, dezocine, nalorphine, cyclazocine and pharmaceutically acceptable salts thereof.

25. The analgesic composition of Claim 20 containing a therapeutically effective amount of at least one other pharmacologically active substance (c).

26. The analgesic composition of Claim 25 wherein the pharmacologically active substance (c) is a non-narcotic analgesic.

27. The analgesic composition of Claim 26 wherein the non-narcotic analgesic is selected from the group consisting of acetaminophen, aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufensial, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin and zomepirac.

28. The analgesic composition of Claim 20 wherein (a) and (b) are present in sustained release dosage form.

INTERNATIONAL SEARCH REPORT

Inte .tional Application No
PCT/US 98/24045

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K31/485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 06708 A (MCLAUGHLIN KATHLEEN T ;MEDICH JOHN R (US); SEARLE & CO (US); TALLE) 19 February 1998 (1998-02-19) *see claims 5,6,9; page 2, lines 6-13; page 14, line 34 - page 15, line 16* ---	1,2, 4-11, 13-21, 23-28
X	WO 97 38986 A (GRANETO MATTHEW J ;BROWN DAVID L (US); SEARLE & CO (US); TALLEY JO) 23 October 1997 (1997-10-23) *see in particular pages 3-7, 112-115; claims 39,60 * --- -/--	1,2, 8-11,13, 18-21, 24,28

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
27 July 1999	12/08/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inte .ional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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E	WO 99 21585 A (UNION PHARMA SCIENT APPL) 6 May 1999 (1999-05-06) *see in particular the claims; examples 3,4; Figures 5,7,9,11*	1-3, 5-13, 15-23, 25-28
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